

INTERNATIONAL SEARCH REPORT

Inter	Intl Application No
PCT/US 94/10080	

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C12N15/12 C07K14/71 C07K14/51 C07K16/28 A61K38/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO,A,94 11502 (LUDWIG INSTITUTE FOR CANCER RESEARCH, GB) 26 May 1994 see the whole document ---	1-36
P,X	WO,A,93 19177 (THE GENERAL HOSPITAL CORP; US) 30 September 1993 see the whole document ---	3,5,9, 20-28
X	DEVELOPMENTAL DYNAMICS, vol.196, no.2, February 1993, US pages 133 - 142 HE, W.H. ET AL.; 'Developmental expression of four novel serine/threonine kinase receptors homologous to the activin/transforming growth factor-beta type II receptor family' see the whole document --- -/--	3,5,9, 20-29

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

20 December 1994

Date of mailing of the international search report

30.12.94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Nauche, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,91 18047 (GEENETECH, INC.; US) 28 November 1991 see the whole document ----	37-52
X	WO,A,88 00205 (GENETICS INSTITUTE, INC.; US) 14 January 1988 see the whole document ----	37-52
X	EP,A,0 416 578 (TADEKA CHEMICAL INDUSTRIES, LTD.; JP) 13 March 1991 see the whole document ----	37-52
X	PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA., vol.89, December 1992, WASHINGTON US pages 11740 - 11744 CUNNINGHAM, N.S. ET AL.; 'Osteogenin and recombinant bone morphogenetic protein 2B are chemotactic for human monocytes and stimulate transforming growth factor beta1 m RNA expression' see the whole document -----	37-52

INTERNATIONAL SEARCH REPORT

Information on patent family members

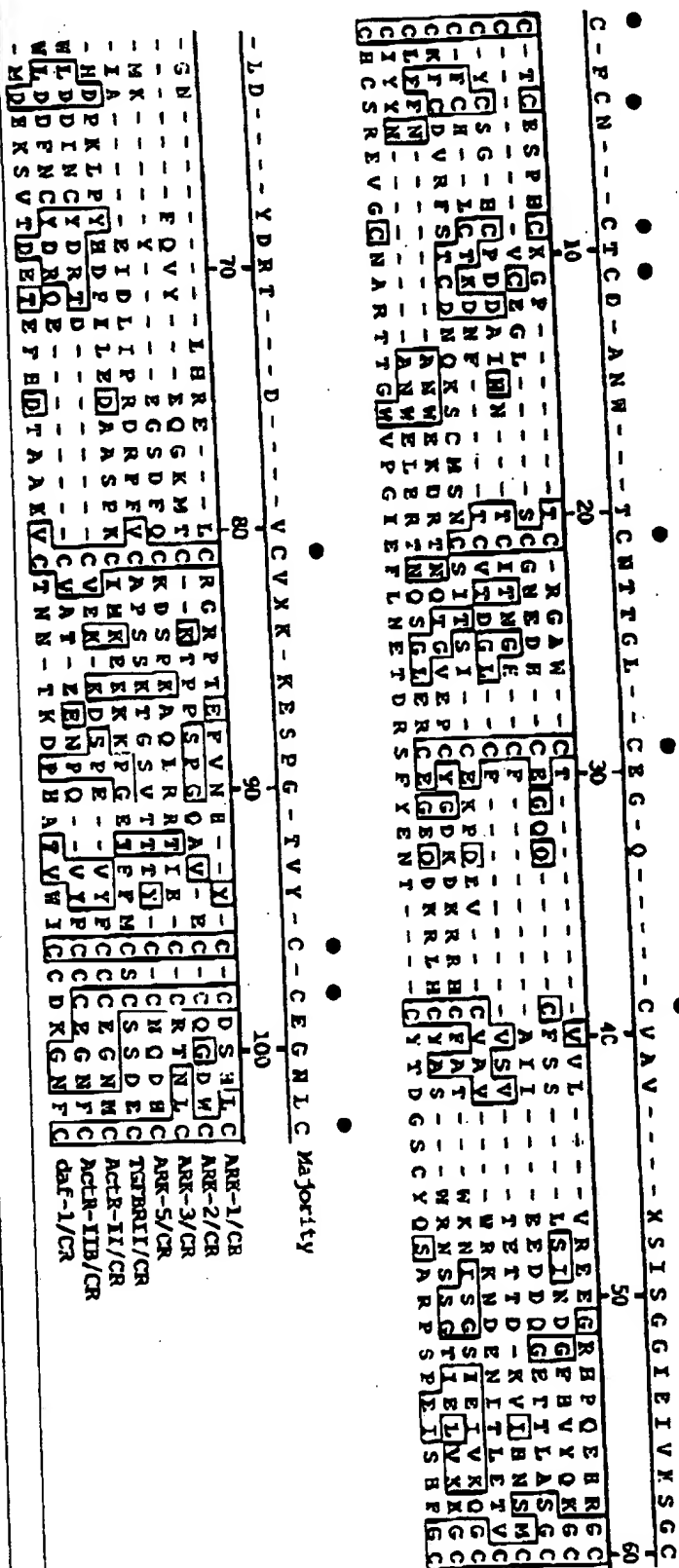
International Application No

PCT/US 94/10080

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9411502	26-05-94	AU-B- 5432094	08-06-94
WO-A-9319177	30-09-93	AU-B- 3920693	21-10-93
WO-A-9118047	28-11-91	US-A- 5168050	01-12-92
		AT-T- 114163	15-12-94
		EP-A- 0531448	17-03-93
WO-A-8800205	14-01-88	US-A- 4877864	31-10-89
		AU-B- 613314	01-08-91
		AU-A- 7783587	29-01-88
		EP-A- 0313578	03-05-89
		JP-A- 6298800	25-10-94
		JP-T- 2500241	01-02-90
		US-A- 5013649	07-05-91
		US-A- 5166058	24-11-92
		US-A- 5187076	16-02-93
		US-A- 5116738	26-05-92
		US-A- 5366875	22-11-94
		US-A- 5106748	21-04-92
		US-A- 5108922	28-04-92
		US-A- 5141905	25-08-92
EP-A-0416578	13-03-91	JP-A- 4154799	27-05-92

[illegible]

ALIGNMENT OF CYSTEINE RICH DOMAINS



PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

RECEIVED

GILL JENNINGS & EVERY

Broadgate House

7 Eldon Street

London EC2M 7LH

ROYAUME-UNI

- 6 JUN 1994

GILL JENNINGS & EVERY

Date of mailing:

26 May 1994 (26.05.94)

Applicant's or agent's file reference:

70/4201/03

IMPORTANT NOTICE

International application No.:

PCT/GB93/02367

International filing date:

17 November 1993 (17.11.93)

Priority date:

17 November 1992 (17.11.92)

Applicant:

LUDWIG INSTITUTE FOR CANCER RESEARCH et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, CA, EP, JP, KR, NZ, US

2. In accordance with Rule 47.1(c), third sentence, each Designated Office will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Offices.
3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on

26 May 1994 (26.05.94) under No. WO 94/11502

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

Entered by

Records on

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorised officer:

J. Zappa

Telephone No.: (41-22) 730.9.11

- 6 JUN 1994

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
UNITED KINGDOM

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing

(day;month;year) X 20. 05. 94

Applicant's or agent's file reference

70/4201/03

FOR FURTHER ACTION See paragraphs 1 and 4 below

International application No.

PCT/GB93/02367

International filing date

(day;month;year) 17/11/93

Applicant

LUDWIG INSTITUTE FOR CANCER RESEARCH et al.

1. ☒ The applicant is hereby notified that the international search report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the international search report; however, for more details, see the notes on the accompanying sheet.

Where? To the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2; the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicants's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau.

If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Entered by
Records on:

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

NUTRIBIO

23 MAY 1994

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 70/4201/03	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/GB93/02367	International filing date (day/month/year) 17/11/93	(Earliest) Priority Date (day/month/year) 17/11/92
Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING SERINE/THREONINE KINASE DOMAINS AND THEIR USES.

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. 1 ☐ as suggested by the applicant.

☐ None of the figures.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

PCT/GB 93/02367

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C12N15/12 C07K13/00 C12N5/10 A61K37/00 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>ONCOGENE vol. 8, no. 10, October 1993, GB pages 2879 - 2887 TEN DIJKE P; ICHIJO H; FRANZEN P; SCHULZ P; SARAS J; TOYOSHIMA H; HELDIN C-H; MIYAZONO K; 'ACTIVIN RECEPTOR-LIKE KINASES A NOVEL SUBCLASS OF CELL-SURFACE RECEPTORS WITH PREDICTED SERINE-THREONINE KINASE ACTIVITY' see the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-31

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

25 April 1994

Date of mailing of the international search report

20. 05. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3616

Authorized officer

Nauche, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with location, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL vol. 68 , 21 February 1992 , CAMBRIDGE, NA US pages 775 - 785 LIN, H.Y. ET AL.; 'Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/threonine kinase' see the whole document ----	1-31
A	CELL vol. 65 , 14 June 1991 , CAMBRIDGE, NA US pages 973 - 982 MATHEWS LS;VALE WW; 'Expression cloning of an activin receptor, a predicted transmembrane serine kinase.' see the whole document ----	1-31
A	SCIENCE vol. 255 , 27 March 1992 , LANCASTER, PA pages 1702 - 1705 MATHEWS, L.S. ET AL.; 'Cloning of a second type of activin receptor and functional characterization in Xenopus Embryos.' see the whole document ----	1-31
A	CELL vol. 68 , 10 January 1992 , CAMBRIDGE, NA US pages 97 - 108 ATTISANO L;WRANA JL;CHEIFETZ S;MASSAGUE J; 'Novel activin receptors: distinct genes and alternative mRNA splicing generate a repertoire of serine/threonine kinase receptors.' see the whole document -----	1-31

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty.

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 70/4201/03	
International application No. PCT/GB93/02367	International filing date (day/month/year) 17.11.93
(Earliest) Priority date (day/month/year) 17.11.92	
Title of invention ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING SERINE THREONINE KINASE DOMAINS AND THEIR USE	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) LUDWIG INSTITUTE FOR CANCER RESEARCH St. Mary's Hospital Medical School Norfolk Place Paddington London W2 1PG United Kingdom	
Telephone No.:	
Facsimile No.:	
Teleprinter No.:	
State (i.e. country) of nationality: United Kingdom	State (i.e. country) of residence: United Kingdom
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MIYAZONO, Kohei Flogstavägen 63D S-752 63 Uppsala Sweden	
State (i.e. country) of nationality: Japan	State (i.e. country) of residence: Sweden
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) DIJKE, Peter ten Flogstavägen 25C S-752 63 Uppsala Sweden	
State (i.e. country) of nationality: Netherlands	State (i.e. country) of residence: Sweden
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet is not to be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

FRANZEN, Petra
Lindsbergsgatan 15b
S-752 40 Uppsala
Sweden

State (i.e. country) of nationality:
Sweden

State (i.e. country) of residence:
Sweden

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

YAMASHITA, Hidetoshi
Flogstavägen 33A
S-752 63 Uppsala
Sweden

State (i.e. country) of nationality:
Japan

State (i.e. country) of residence:
Sweden

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

HELDIN, Carl-Henrik
Hesselmanns väg 35
S-752 63 Uppsala
Sweden

State (i.e. country) of nationality:
Sweden

State (i.e. country) of residence:
Sweden

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (i.e. country) of nationality:

State (i.e. country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GILL JENNINGS & EVERY
 Broadgate House
 7 Eldon Street
 London
 EC2M 7LH
 United Kingdom

Telephone No.:

071 377 1377

Facsimile No.:

071 377 1310

Teleprinter No.:

22765

☐ Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV STATEMENT CONCERNING AMENDMENTS

The applicant wishes the International Preliminary Examining Authority*

- (i) ☐ to start the international preliminary examination on the basis of the international application as originally filed.
- (ii) ☐ to take into account the amendments under Article 34 of
- ☐ the description (amendments attached).
 - ☐ the claims (amendments attached).
 - ☐ the drawings (amendments attached).
- (iii) ☐ to take into account any amendments of the claims under Article 19 filed with the International Bureau (a copy is attached).
- (iv) ☐ to disregard any amendments of the claims made under Article 19 and to consider them as reversed.
- (v) ☐ to postpone the start of the international preliminary examination until the expiration of 20 months from the priority date unless that Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

- * Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Box No. V ELECTION OF STATES

- ☒ The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)* except.....

(If the applicant does not wish to elect certain eligible States, the name(s) or country code(s) of those States must be indicated above.)

Box No. VI CHECK LIST

The demand is accompanied by the following documents for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. amendments under Article 34 | | |
| description | : | sheets |
| claims | : | sheets |
| drawings | : | sheets |
| 2. letter accompanying amendments under Article 34 | : | sheets |
| 3. copy of amendments under Article 19 | : | sheets |
| 4. copy of statement under Article 19 | : | sheets |
| 5. other (specify): | : | sheets |

For International Preliminary Examining Authority use only

received not received

<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. <input type="checkbox"/> separate signed power of attorney | 4. <input type="checkbox"/> fee calculation sheet |
| 2. <input type="checkbox"/> copy of general power of attorney | 5. <input type="checkbox"/> other (specify): |
| 3. <input type="checkbox"/> statement explaining lack of signature | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

GILL JENNINGS & EVERY
Agents for the Applicants

R E Perry

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.

☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

GILL JENNINGS & EVERY

Date of mailing
(day/month/year) 22.09.94

Applicant's or agent's file reference
70/4201/03

REPLY DUE within 3 months/days
from the above date of mailing

International application No. PCT/GB 93/ 02367	International filing date (day/month/year) 17/11/1993	Priority date (day/month/year) 17/11/1992
---	--	--

International Patent Classification (IPC) or both national classification and IPC
C12N15/12

Applicant
LUDWIG INSTITUTE FOR CANCER RESEARCH et al.

1. This written opinion is the first (first, etc.) drawn up by this International Preliminary Examining Authority.

2. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).


How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 17/03/1995

Entered by
Records on:
26 SEP 1994
[Signature]

 <p>European Patent Office D-80298 Munich Tel. (+ 49-89) 2399-0, Tx: 523656 epmu d Fax: (+ 49-89) 2399-4465</p>	<p>Name and mailing address of the IPEA/</p>	<p>Authorized officer Examiner [Signature] G. Alt</p>
	<p>Formalities officer (incl. extension of time limits) Telephone No. 5052</p>	<p>C. Vullo [Signature]</p>

I. Basis of the opinion

1. This opinion has been drawn up on the basis of:

☒ the international application as originally filed.

☐ the description, pages _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,

☐ the claims, No. _____, as originally filed,
No. _____, as amended under Article 19,
No. _____, filed with the demand,
No. _____, filed with the letter of _____,

☐ the drawings, sheets/fig _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,

2. The amendments have resulted in the cancellation of: pages: _____
sheets of drawings/figures No.: _____.

3. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed:

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-31 _____

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 1-31 _____ are so unclear that no meaningful opinion could be formed (specify):

see this Written Opinion, section V, 1. and VIII, 1.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims _____
	Claims _____
Inventive Step (IS)	Claims _____
	Claims _____
Industrial Applicability (IA)	Claims _____
	Claims _____

2. CITATIONS AND EXPLANATIONS

1. The fact that the proteins of the invention are defined in the claims in various ways and some of them in an unclear manner leads to doubts as to what the invention actually is. Therefore a meaningful examination as to novelty and inventive step can only take place once the claims have been redrafted (see item VIII, 1. of this Written Opinion).

As far as the claims are understood the following preliminary opinion on the question of novelty of some of the claims is given:

- 1.1 Claims 1 and 2 appear to be novel due to the specific sequences in subdomain VIB and subdomain VIII.
- 1.2 Proteins falling within the scope of Claims 3 - 5 appear to exist, see the sequence comparison of Figure 1 of the present application.
- 1.3 Claims 6 and 8 appear to be novel.
-

- 1.4 The subject-matter of Claims 7 and 9 appears to be anticipated by the publications mentioned on page 3, lines 7-21 of the application.

2. The priority documents pertaining to the present application were not available at the time of establishing this first written opinion. Hence, it is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document Oncogene, vol.8, no.10, october 1993, pp. 2879-2887 cited in the international search report could become relevant to assess whether claims 1-31 satisfy the criteria set forth in Article 33(1) PCT.

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1. The various definitions of the invention given in independent Claims 1, 3, 6, 7, 8 and 9 are such that the claims as a whole are not clear and concise, contrary to Article 6 PCT. The claims should be recast to include only the minimum necessary number of independent claims in this category, with dependent claims as appropriate (Rule 6.4(a)-(c) PCT).

In the present case it is considered appropriate to use only one independent claim in the "protein-category".

2.

- 2.1 In the claims the term "serine/threonine kinase domain" as such is unclear (Article 6 PCT). It should be clarified by explaining that it was identified on the basis of sequence similarities between daf-1 gene product, activin type II receptor and TGF- β type II receptor (see page 18, last full paragraph). Moreover, the position of the domain in these proteins should be indicated.

- 2.2 Moreover the term "serine/threonine kinase domain" should be clarified in the claims to read "receptor serine/threonine kinase domain".

3. It should be made clear throughout the claims that the subdomains are subdomains of the receptor serine/threonine kinase domain (Article 6 PCT).

4. In Claim 6 the term "more than 50% identity" is not clear (Article 6 PCT) without an indication of the

length of the protein stretch where the identity is to occur.

The same objection applies *mutuatis mutandis* to Claim 4.

Gill Jennings & Every

European Patent Attorneys
Trade Mark Attorneys

Broadgate House · 7 Eldon Street · London EC2M 7LH

Telephone: 0171-377 1377
Telex: 22765 GILPAT G

Fax: 0171-377 1310
Email: gje@gje.co.uk

PAUL BRUNNER
M J BRUNNER
RADI
RE PERRY
R E SKONE JAMES
H M M JONES
A H LARO
R C BERCON
N HOPE
M V GOR
P W HARRIS
J EET
C J CURVEN
S WELLS
A FLINT
M J DRAPER
Accounts L K DOLTON
Records: Trade Marks N D STANTON
Computer Systems G G ANABILINO
Patents G M ALDERMAN

The European Patent Office
Erhardtstrasse 27
D-80298 Munich
Germany

Our Ref. 70/4201/03

Your Ref. 23rd January 1995

BY FACSIMILE
CONFIRMATION BY POST

PCT Chapter II
MU DG2

Dear Sirs

International Patent Application No. PCT/GB93/02367
Ludwig Institute For Cancer Research, et al

In response to the Written Opinion dated 22.09.94, a replacement page 83 is filed herewith in triplicate, including amended claims 1-3, 7 and 9. The Applicants do not intend to make any amendment to the description in the international phase.

Claims 1 and 3 have been amended by the addition of "receptor" in their respective first lines. This amendment satisfies Section VIII(2.2).

Claim 1 has been amended by indicating the correspondence between the relevant domain and those in other products. This satisfies VIII(2.1).

The phrase "of said domain" has been added twice in each of claims 1 and 2. This satisfies Section VIII(3).

Claims 3, 7 and 9 have been amended to specify that the protein has "a GS box" (Gly-Ser repeat). This motif can be seen in Figure 3 page 4/11 in the third block of compared sequences. The proteins of this invention (defined as A1.Ks 1-6 etc) contain this "box" but the type II receptor sequences that are compared to it (first three lines of sequences) do not. For claims 7 and 9 at least, this amendment ensures that the claims relate to novel subject matter.

Finally, claims 7 and 9 have been amended by the removal of previous characteristic (ii), in each case. Activin-binding activity is not associated with the isolated proteins of claims 7 and 9; the Type I receptors have to bind to type II receptors in order to have activin-binding activity, and therefore this activity has been used to characterise what was previously given as characteristic (iii) in each case.

The proteins of the invention (ALKs 1-6 etc) are type I receptor proteins for TGF- β and other members of the TGF- β superfamily, e.g. activin. Figure 1 also shows an alignment of type II receptor proteins from which several motifs and functional domains can be identified. Both type I and II receptor proteins have a serine/threonine kinase domain as defined in claims 3, 4 and 5, but any less than 50% identity in this domain would include type II receptor sequences. Therefore, the claims are specific for the type I receptor sequences of the invention. On page 4, lines 1-6 of the specification, sequence similarities between the type I and type II receptor kinase domains are given as 33-39%. In contrast, within the type I receptor family, the similarity in the kinase domains is 40-92%. Therefore, the 50% identity is a conservative figure.

Section VIII(4) of the Written Opinion should presumably have referred to claims 3 and 4. In the light of the explanation given above, and since "identity" is an unambiguous term, it is denied that these claims lack clarity. Further, with respect to Section VIII(1), it is denied that there is lack of clarity because different definitions are used in various independent claims. It is not necessarily appropriate to use only one independent claim, if the Applicants are entitled to claim the invention in more than one way. In particular, it is submitted that the application of Article 6 PCT is inappropriate, since each claim is in itself quite clear.

Please date-stamp and return the attached Form 1037 to me, as acknowledgement of receipt.

Yours faithfully
GILL JENNINGS & EVERY


R. E. Perry
(Named Representative)

CLAIMS

1. An isolated protein having a receptor serine/threonine kinase domain corresponding to that in daf-1 gene product, activin type II receptor and TGF- β type II receptor, a
5 DFKSKN or DLKSKN sequence in subdomain VIB of said domain and/or a GTKRYM sequence in subdomain VIII of said domain.
2. A protein according to claim 1, which additionally comprises an ATP-binding sequence that is Gly-Xaa-Gly-Xaa-Xaa-Gly in subdomain I of said domain, and a Lys residue in
10 subdomain II of said domain.
3. An isolated protein having a GS box and a receptor serine/threonine kinase domain which has more than 50% identity to the kinase domain of any of the amino-acid sequences identified herein as SEQ ID. Nos. 2, 4, 6, 8, 10,
15 12, 14, 16 and 18.
4. A protein according to claim 3, wherein the identity is more than 60%.
5. A protein according to any preceding claim, having serine/threonine kinase activity.
- 20 6. An isolated protein having all or part of any of the amino-acid sequences identified herein as SEQ. ID Nos. 2, 4, 6, 8, 10, 12, 14, 16 and 18, and activin receptor type I functionality.
7. An isolated protein having a GS box and an amino-acid sequence corresponding to part or all of the amino-acid
25 sequence of an activin type I receptor, and wherein the protein has serine/threonine kinase activity and/or activin type II receptor interaction providing activin-binding activity.
- 30 8. An isolated protein having a GS box and all or part of any of the amino-acid sequences identified herein as SEQ. ID Nos. 2, 4, 6, 8, 10, 12, 14, 16 and 18, and TGF- β -type I receptor functionality.
9. An isolated protein having an amino-acid sequence
35 corresponding to part or all of the amino-acid sequence of a TGF- β -type I receptor, and wherein the protein has serine/threonine kinase activity and/or TGF- β -type II receptor interaction providing TGF- β -binding activity.

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

GILL JENNINGS & EVERY :
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

13. 03. 95

Applicant's or agent's file reference
70/4201/03

IMPORTANT NOTIFICATION

International application No.

PCT/GB 93/ 02367

International filing date (day/month/year)

17/11/1993

Priority date (day/month/year)

17/11/1992

Applicant

LUDWIG INSTITUTE FOR CANCER RESEARCH et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

Please note therefore that International Preliminary Examination Report issued 17.03.95 is to be considered as null and void and is replaced by the Report hereby attached!

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Annex

from IPEA 404

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

H. P. Dietenhofer

Telephone No.

H.-P. Dietenhofer

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

GILL JENNINGS & EVERY
Broadgate House
7 Eldon Street
LONDON EC2M 7LH
GRANDE BRETAGNE

COMMUNICATION IN CASES FOR WHICH
NO OTHER FORM IS APPLICABLE

Date of mailing
(day/month/year)

13. 03. 95

Applicant's or agent's file reference

70/4201/03

REPLY DUE

See paragraph 1 below

International application No.

PCT/GB 93/ 02367

International filing date (day/month/year)

17/11/1993

Applicant

LUDWIG INSTITUTE FOR CANCER RESEARCH et al.

1. ☐ REPLY DUE within _____, months/days from the above date of mailing
☒ NO REPLY DUE

2. COMMUNICATION:

1. The IPEA apologizes for the factual errors in the IPER dated 17.02.95 and for any inconveniences this may have caused. In the newly issued IPER these errors have been corrected.
2. The IPEA has considered your observations concerning the objection of lack of unity. In the Written Opinion dated 22.09.94, section VIII, 1., it was pointed out that a lack of clarity existed due to the presence of too many independent claims. However, a formal objection of lack of unity was raised for the first time in the IPER. It is acknowledged that the Applicants did not have the possibility to give their opinion on this point. In view of the above, the objection of lack of unity is no longer pursued in the PCT-phase and has been deleted from the IPER.
It is however noted that the IPEA still considers that there is a lack of unity of invention.

Name and mailing address of the IPEA/



European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Telephone No.

G. AIT

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 70/4201/03	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/GB 93/ 02367	International filing date (day/month/year) 17/11/1993	Priority date (day/month/year) 17/11/1992
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


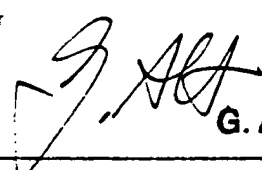
2. This REPORT consists of a total of 4 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of 1 sheets.

3. This report contains indications and corresponding pages relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 09/06/1994	Date of completion of this report 13. 03. 95
Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+ 49-89) 2399-0, Tx: 523656 epimu d Fax: (+ 49-89) 2399-4465	Authorized officer  G. Alt Telephone No.

I. Basis of the report

1. This report has been drawn up on the basis of (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):

☐ the international application as originally filed.

☒ the description, pages 1-34, 35-82 (sequence listing) _____, as originally filed,
pages _____, filed with the demand,
pages _____, filed with the letter of _____,
pages _____, filed with the letter of _____.

☒ the claims, Nos. 10-31 _____, as originally filed,
Nos. _____, as amended under Article 19,
Nos. _____, filed with the demand,
Nos. 1-9 _____, filed with the letter of 23/01/95,
Nos. _____, filed with the letter of _____.

☒ the drawings, sheets/fig 1/8-8/8 _____, as originally filed,
sheets/fig _____, filed with the demand,
sheets/fig _____, filed with the letter of _____,
sheets/fig _____, filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

☐ the description, pages _____.
☐ the claims, Nos. _____.
☐ the drawings, sheets/fig _____.

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-31_____

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination (specify):

☒ the description, claims or drawings (indicate particular elements below) or said claims Nos. 1-31_____ are so unclear that no meaningful opinion could be formed (specify):

Article 6 PCT requires that the claims shall be concise; this refers to individual claims as well as to the claims in their entirety (see the PCT-Guidelines, CIII, 5.1).

Moreover, Article 6 PCT taken in combination with Rule 6(3)(b) PCT requires that any independent claim must contain all the technical features essential to the invention, i.e. all those features which distinguish the claimed subject-matter from subject-matter disclosed in the prior art.

The present invention is set out in six independent claims relating to isolated proteins. These six claims provide six differently worded, non-analogous definitions (see Claims 1, 3, 6-9). There is no non-obvious, technical feature which is common to all these alternative definitions. This presentation makes it impossible to determine what the essential technical features are of the matter for which protection is sought. Therefore,

the present set of claims does not meet the
clarity-requirements of Article 6 PCT.

[] the claims, or said claims Nos. _____ are so inadequately supported by
the description that no meaningful opinion could be formed.

[] no international search report has been established for said claims
Nos. _____.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 70/4201/03	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/GB93/02367	International filing date (day/month/year) 17/11/93	(Earliest) Priority Date (day/month/year) 17/11/92
Applicant LUDWIG INSTITUTE FOR CANCER RESEARCH et al.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☐ Certain claims were found unsearchable (see Box I).

2. ☐ Unity of invention is lacking (see Box II).

3. ☒ The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing

☐ filed with the international application.

☒ furnished by the applicant separately from the international application,

☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.

☐ Transcribed by this Authority

4. With regard to the title, ☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING SERINE/THREONINE KINASE DOMAINS AND THEIR USES.

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is:

Figure No. 1 ☐ as suggested by the applicant.

☐ None of the figures.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

National Application No

GB 93/02367

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C12N15/12 C07K13/00 C12N5/10 A61K37/02 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ONCOGENE vol. 8, no. 10 , October 1993 , GB pages 2879 - 2887 TEN DIJKE P; ICHIJO H; FRANZEN P; SCHULZ P; SARAS J; TOYOSHIMA H; HELDIN C-H; MIYAZONO K; 'ACTIVIN RECEPTOR-LIKE KINASES A NOVEL SUBCLASS OF CELL-SURFACE RECEPTORS WITH PREDICTED SERINE-THREONINE KINASE ACTIVITY' see the whole document --- -/--	1-31



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

25 April 1994

Date of mailing of the international search report

20. 05. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Nauche, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CELL vol. 68 , 21 February 1992 , CAMBRIDGE, NA US pages 775 - 785 LIN, H.Y. ET AL.; 'Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/threonine kinase' see the whole document ---	1-31
A	CELL vol. 65 , 14 June 1991 , CAMBRIDGE, NA US pages 973 - 982 MATHEWS LS;VALE WW; 'Expression cloning of an activin receptor, a predicted transmembrane serine kinase.' see the whole document ---	1-31
A	SCIENCE vol. 255 , 27 March 1992 , LANCASTER, PA pages 1702 - 1705 MATHEWS, L.S. ET AL.; 'Cloning of a second type of activin receptor and functional characterization in Xenopus Embryos.' see the whole document ---	1-31
A	CELL vol. 68 , 10 January 1992 , CAMBRIDGE, NA US pages 97 - 108 ATTISANO L;WRANA JL;CHEIFETZ S;MASSAGUE J; 'Novel activin receptors: distinct genes and alternative mRNA splicing generate a repertoire of serine/threonine kinase receptors.' see the whole document -----	1-31

PATENT COOPERATION TREATY

PCT

COMMUNICATION OF
INTERNATIONAL APPLICATIONS

(PCT Article 20)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
Washington, D.C.

Date of mailing:

07 July 1994 (07.07.94)

in its capacity as designated Office

The International Bureau transmits herewith copies of the international applications having the following international application numbers and international publication numbers:

International application no.:

PCT/GB93/02367

International publication no.:

WO94/11502

**CORRECTED VERSION
VERSION CORRIGEE**

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer:

J. Zahra

Telephone No.: (41-22) 730.91.11



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C12N 15/12, C07K 13/00 C12N 5/10, A61K 37/02 G01N 33/68		A3	(11) International Publication Number: WO 94/11502 (43) International Publication Date: 26 May 1994 (26.05.94)
(21) International Application Number: PCT/GB93/02367 (22) International Filing Date: 17 November 1993 (17.11.93) (30) Priority data: 9224057.1 17 November 1992 (17.11.92) GB 9304677.9 8 March 1993 (08.03.93) GB 9304680.3 8 March 1993 (08.03.93) GB 9311047.6 28 May 1993 (28.05.93) GB 9313763.6 2 July 1993 (02.07.93) GB 9316099.2 3 August 1993 (03.08.93) GB 9321344.5 15 October 1993 (15.10.93) GB (71) Applicant (for all designated States except US): LUDWIG INSTITUTE FOR CANCER RESEARCH [GB/GB]; St. Mary's Hospital Medical School, Norfolk Place, Pad- dington, London W2 1PG (GB).		(72) Inventors; and (75) Inventors/Applicants (for US only): MIYAZONO, Kohei [JP/SE]; Flogstavägen 63D, S-752 63 Uppsala (SE). DIJKE, Peter, Ten [NL/SE]; Flogstavägen 25C, S-752 63 Uppsala (SE). FRANZEN, Petra [SE/SE]; Linds- bergsgatan 15b, S-752 40 Uppsala (SE). YAMASHITA, Hidetoshi [JP/SE]; Flogstavägen 33A, S-752 63 Uppsala (SE). HELDIN, Carl-Henrik [SE/SE]; Hesselmans väg 35, S-752 63 Uppsala (SE). (74) Agent: GILL JENNINGS & EVERY; Broadgate House, 7 Eldon Street, London EC2M 7LH (GB). (81) Designated States: AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments. (88) Date of publication of the international search report: 7 July 1994 (07.07.94)	

(54) Title: ACTIVIN RECEPTOR-LIKE KINASES, PROTEINS HAVING SERINE/THREONINE KINASE DOMAINS AND THEIR USE

cons.aa	G G G V	A K	E
hTGFB- II	LDTLVGKGRFAEVYKAKLKQNTSEQFETVAVKIFPYDHYASWDRKDI FSDINLKHENILQF		
mActR- IIB	LLEIKARGRFQCVWKAQLMN-----DFVAVKIKPLQDKQSWQSEREI FSTPGMKHENLLQF		
mActR- II	LLEVKARGRFQCVWKAQLLN-----EYVAVKIPFIQDKQSWQNEYEVYSI PGMKHENILQF		
daf- I	LTVRGSGRFGNVSRGDYRG-----EAVAVKVFNAIDEPAFHKEIEI FETRMRLRHPNVRLRY		
subdomains	I	II	III IV

hTGFB- II	LTAEERKTELGKQYWLITAFHAKGNLQEYLTRHVISWEDLRNVGSSSLARGLSHLSDHTP-C
mActR- IIB	IAAEKRGSNLEVELWLI TAFHDKGSLIDYLGKNI ITWNELCVHAETMSRGI SYLHEDVWPWR
mActR- II	IGAERGTSDVDLWLI TAFHEKGSLSDFLKANVSWNELCHIAETMARGLAYLHEDI PGLK
daf- I	IGSDRVDTGFTLWLVIEYHPGSLHDFLENTVNI ETYYNLMRSTASGLAFLHNQIGGSK
subdomains	V VI-A

cons.aa	DLK N	DFG
hTGFB- II	-GRPKMPIVHRDLKSSNLLVRNDLTCCLCD FGLSLRL ---GPYSSVDDLANSQGVGTARYMAP	
mActR- IIB	GEHGKPSIAHRDFKSKNVLLKNSDLTAVLADFGLAVRF ---EPGKPPGD ---THGQVGTTRYMAP	
mActR- II	-DGHKPAISHRDIKSKNVLLKNNLTACIADFGLALKF ---EAGKSAGD ---THGQVGTTRYMAP	
daf- I	-ESNKPAMAHARDIKSKNIMYKNDLTCAIGDLGLSLSKPEDAASDI IAN ---ENYKCGTVRYLAP	
subdomains	VI-B VII VIII	

(57) Abstract

A new receptor family has been identified, of activin-like kinases. Novel proteins have activin/TGF- β -type I receptor functionality, and have consequential diagnostic/therapeutic utility. They may have a serine/threonine kinase domain, a DFKSRN or DLKSKN sequence in subdomain VIB and/or a GTKRYM sequence in subdomain VIII.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CELL vol. 68 , 21 February 1992 , CAMBRIDGE, NA US pages 775 - 785 LIN, H.Y. ET AL.; 'Expression cloning of the TGF-beta type II receptor, a functional transmembrane serine/threonine kinase' see the whole document ---</p>	1-31
A	<p>CELL vol. 65 , 14 June 1991 , CAMBRIDGE, NA US pages 973 - 982 MATHEWS LS;VALE WW; 'Expression cloning of an activin receptor, a predicted transmembrane serine kinase.' see the whole document ---</p>	1-31
A	<p>SCIENCE vol. 255 , 27 March 1992 , LANCASTER, PA pages 1702 - 1705 MATHEWS, L.S. ET AL.; 'Cloning of a second type of activin receptor and functional characterization in Xenopus Embryos.' see the whole document ---</p>	1-31
A	<p>CELL vol. 68 , 10 January 1992 , CAMBRIDGE, NA US pages 97 - 108 ATTISANO L;WRANA JL;CHEIFETZ S;MASSAGUE J; 'Novel activin receptors: distinct genes and alternative mRNA splicing generate a repertoire of serine/threonine kinase receptors.' see the whole document -----</p>	1-31

INTERNATIONAL SEARCH REPORT

National Application No.

PCT/GB 93/02367

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C12N15/12 C07K 3/00 C12N5/10 A61K37/00 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C12N C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	ONCOGENE vol. 8, no. 10 , October 1993 , GB pages 2879 - 2887 TEN DIJKE P; ICHIJO H; FRANZEN P; SCHULZ P; SARAS J; TOYOSHIMA H; HELDIN C-H; MIYAZONO K; 'ACTIVIN RECEPTOR-LIKE KINASES A NOVEL SUBCLASS OF CELL-SURFACE RECEPTORS WITH PREDICTED SERINE-THREONINE KINASE ACTIVITY' see the whole document --- -/--	1-31

☒ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

25 April 1994

Date of mailing of the international search report

20. 05. 94

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Nauche, S